immunodeficiency virus type 1 (HIV-1), human immunodeficiency virus type 2 (HIV-2), or simian immunodeficiency virus (SIV_{agm}).

17. A method of inactivating lipid-enveloped viruses in cell cultures which comprises

providing a cyclic lipopeptide, a salt of the lipopeptide, an ester of the lipopeptide, or a mixture thereof;

contacting said cell culture with the cyclic lipopeptide, salt of the lipopeptide, ester of the lipopeptide, or mixture thereof as an inactivating agent, at room temperature for between 3-8 days wherein the agent is added to the cell culture at a concentration of 1-65μM.--

REMARKS

New claims 13-17 have been added to the specification. Support for these new claims may be found in original claims 1, 2, 6 and 10. Further support for new claim 17 may be found in Example 9 of the specification. These new claims in no way add new matter to the specification. As such, entry and consideration thereof are respectfully requested.

Information Disclosure Statement

The Examiner states that the Information Disclosure Statement filed on April 12, 1999 fails to comply with 37 C.F.R. §1.98(a)(3) because it does not contain a concise explanation of relevance. Specifically, the Examiner notes that she has not considered reference DE 19521938 because it is not in English.

Applicants respectfully note that the reference DE '938 was cited by the

international Examiner and is contained as a reference in the English-language International Search Report with an indication of relevance ("P,A"). Under M.P.E.P. § 609(A)(3),

> Where the information listed is not in the English language but was cited in a search report or other action by a foreign patent office in a counter part foreign application, the requirement for a concise explanation of relevance can be satisfied by submitting an English-language version of the search report or action which indicates the degree of relevance found by the foreign patent office. This may be...merely an "A", "Y", or "A" indication on the search report.

Thus, the submission of the Information Disclosure Statement of April 12, 1999 is in full compliance with 37 C.F.R. §1.98(a)(3) and consideration of DE '938 by the Examiner is requested.

Objections to the claims

Claims 1-12 have been objected to for a failing to have a proper introduction. The specification has been amended, as indicated above, to recite "What is claimed is."

Rejections under 35 U.S.C. §112, first pargraph

Claims 1-10 have been rejected under 35 U.S.C. §112, first paragraph for lack of enablement. More specifically, the Examiner asserts that the specification is enabling for inactivating viruses in biological compositions by contacting the compositions with cyclic lipopeptides in concentrations of less than about 10 to 25 μM but not greater than 70μM. The Examiner relies on a teaching of Vollenbroich et al. that the cyclic lipopeptide, surfactin, is lethal at concentrations greater than 70 μM. With regard to the experiments in the specification, the Examiner notes that virus suspended in culture

medium rather than virus infecting cell cultures were used.

Claim 1 has been amended for clarity to recite that when the lipopeptide is added to a culture "medium" at the indicated concentrations. In addition, new claim 17 has been added which is drawn to inactivating virus in cell "cultures" and wherein the lipopeptide concentration has an upper limit of 65μM. This concentration is not lethal to the cells. As such, withdrawal of the rejection is respectfully requested.

Claim 2 has been rejected for lacking enablement of inactivation of viruses at temperatures of 60 °C. The Examiner relies on Horowitz et al. as teaching temperatures of 60 °C result in loss of activity of blood products. Applicants traverse this rejection and withdrawal thereof is respectfully requested. The teaching of Horowitz et al. relied on by the Examiner states, "Although the pasteurization of albumin at 60°C for **10** hours **in the presence of fatty acid ligands** has been reported...."(*emphasis added).*

Claim 2 on the other hand, is drawn to inactivation of viruses using lipopetides within a period of 5-30 min. Thus, the method of claim 2 materially differs from Horowitz et al. in two ways. First, the invention of claim 2 utilizes lipopeptides, whereas Horowitz et al. are treating with fatty acid ligands. Second, the invention of claim 2, uses a maximum incubation of 30 minutes, whereas Horowitz et al. teach that an incubation of 10 hours (20 times longer) was deleterious. As such, the teaching of Horowitz et al. is in no way indicative of a lack of enablement claim 2. Withdrawal of the rejection is, therefore respectfully requested.

Rejections under 35 U.S.C.§112, second paragraph

Claim 1 has been rejected under 35 U.S.C. §112, second paragraph as being indefinite. More specifically, claim 1 has been rejected for failing to recite positive method steps. Claim 1 has been amended to recite positive method steps.

Claim 1 has been further rejected for lacking antecedent basis for "the serum-free culture medium" and "the serum-containing culture medium."

Claims 2, 6, and 10 have been rejected for recitation of "preferably."

Claim 3 has been rejected as being indefinite as to whether any one of naturally occurring, chemically synthesized, or genetically engineered lipopeptides are used in the claimed method or if all are to be used.

Claim 4 has been rejected as requiring a comma between "formula I" and "X."

Claim 5 has been rejected as being indefinite with regard to C_{11}alkyl and C_{12}alkyl and $C_{10\text{-}12}$.

Claim 9 has been rejected for recitation of a broad range (animal) and a narrow included range (human).

Claim 10 has been rejected as being unclear as to whether all the recited viruses are to be simultaneously inactivated. Claim 10 has been further rejected for reciting abbreviations for the viruses and as being unclear as to the metes and bounds of "immunodeficiency viruses" and "herpes viruses."

Claim 11 has been rejected for recitation of "new".

Claim 12 has been rejected as lacking antecedent basis for "lipopeptides" and failing to recite method steps.

Claims 1-12 have been amended or cancelled as indicated above to address the

rejections and clarify the claims. Withdrawal of the rejections is therefore, respectfully requested.

Rejections under 35 U.S.C. 101

Claim 12 has been rejected under 35 U.S.C. §101 as being an improper "use" claim. Claim 12 has been cancelled, thus obviating this rejection.

Rejections under 35 U.S.C. §103

Claims 1, 3, 4-7, 9 and 10 have been rejected under 35 U.S.C.§103 as being obvious over Itokawa et al. Itokawa et al. is asserted to teach surfactins of the present general formula I. Itokawa et al. is asserted to differ from the present invention only in failing to teach contacting the virus with surfactin for 30-120 minutes. However, the Examiner asserts that the time of contact represents routine optimization of the method.

Applicants traverse this rejection and withdrawal thereof is respectfully requested. The sole disclosure in Itokawa et al. regarding antiviral activity is that "they [surfactins 1 and 2] showed moderate anti-HIV activities in XTT formazan assay" See page 607. Itokawa et al. fail to disclose a method inactivating lipid-enveloped viruses in biological products or cell cultures.

Based on the disclosure of Itokawa et al. one skilled in the art would be led away from using cyclic lipopeptides in a method of inactivating lipid-enveloped viruses. The moderate effects of Itokawa et al. are insufficient to safely inactivate viruses to the degree required for biological products for clinical use. The present invention, on the other hand, provides extensive inactivation of lipid-enveloped viruses at low concentrations of

cyclic lipopeptide and with exceedingly short time (30 minutes to 2 hours). As such, the present invention is not simply an "optimization" of Itokawa et al. but provides unexpected, advantageous advantages over Itokawa et al. Withdrawal of the rejection is therefore respectfully requested.

Claims 1, 3, 9 and 10 have been rejected under 35 U.S.C.§103 as being obvious over Naruse et al. Naruse et al. is asserted to teach the inactivation of HSV-1 by contacting the virus with the cyclic lipopeptide, pumilacidin. The Examiner notes that Naruse et al. teach a concentration of pumiliacidin of 3.8 to 6.7 μg/ml compared to the presently recited 1-100μM, but absent a showing to the contrary the concentrations are considered equivalent. The Examiner further asserts that the time of contact represents routine optimization of the method. Applicants traverse this rejection and withdrawal thereof is respectfully requested.

Naruse et al. teach an inhibition of viral-induced cytopathic effects of pumilacidins after 72 hours of incubation. The present method has an upper limit on the incubation time of 2 hours --- a 36-fold difference in time. A 36-fold difference is clearly not simply an "optimization." In addition, 72 hours of incubation results in the modification/degradation of many biological products.

Naruse et al. also present data using pumilacidins on HSV-1 and Vero cells. Pumilacidins are lipoheptapeptides which are related to surfactins but differ in the length of their fatty acid components. For example, some pumilacidins have carbon side chains of 16-17 carbon atoms. Although the inhibitory concentrations of these pumilacidins are comparable to surfactins, the pumilacidins show a higher cytotoxicity. As such, one

skilled in the art would not have been looked to Naruse et al. in developing the present invention.

Thus, the present invention is not simply an "optimization" of Naruse, in that the incubation time is 36-fold less than that of Naruse et al. with unobvious advantages over Naruse et al. in that with a 72 hour incubation may biological products are degraded. In addition, because of the increased cytotoxicity seen with pumilacidins, one skilled in the art would not have considered Naruse et al. in developing the present method. As such, the present invention is clearly not obvious over Naruse et al.

Claim 2 has been rejected under 35 U.S.C. §103 as being obvious over Itokawa et al. or Naruse et al. in view of Horowitz et al. Further to the asserted disclosures of Itokawa et al. and Naruse et al. as discussed above, Horowitz et al. is asserted to teach the increasing the inactivation of viruses in blood derivatives using an organic solvent and a detergent by raising the temperature above room temperature. The Examiner asserts that it would have been obvious to apply the increased temperature of Horowitz et al. to the methods of Itokawa et al. or Naruse et al. Applicants traverse this rejection and withdrawal thereof is respectfully requested.

As discussed above, Horowitz et al. teach treating with fatty acid ligands for an incubation of 10 hours. Horowitz et al. is irrelevant to the presently claimed method of inactivation of lipid-enveloped viruses using lipopeptides. As such, Horowitz et al. fail to teach the deficiencies of the Itokawa et al. and Naruse et al. as discussed above. For example, Horowitz et al. fail to teach an incubation time of at most 2 hours using cyclic

lipopeptides as an efficient means of inactivating lipid-enveloped viruses or the advantages associated therewith. As such, the present invention is not obvious over

Itokawa et al. or Naruse et al. combined with Horowitz et al. Withdrawal of the rejection is therefore respectfully requested.

Claims 8, 11, and 12 have been rejected under 35 U.S.C. §103 as being obvious over Itokawa et al. and Naruse in view of Vater et al. Further to the asserted disclosures of Itokawa et al. and Naruse et al. as discussed above, Vater et al. is asserted to teach that the antiviral activity of lipopetides from *B. subtilis* are produced as mixtures of related variants with similar amino acid compositions but varying in the sequence of their constituents. The Examiner asserts that based on the teachings of Vader the claimed lipopeptides are obvious variants based on these teachings. Applicants traverse this rejection and withdrawal thereof is respectfully requested.

Vater et al. generally disclose antibiotic, antiviral and antitumor activity of lipopeptides. There is no disclosure or suggestion in Vater et al. of the presently claimed method of inactivating lipid-enveloped viruses in biological products or cell cultures, using cyclic peptides as inactivating agents with inactivation at room temperature for 30-120 minutes at the recited concentrations. Thus, the disclosure of Vater et al. is insufficient to teach the omissions of Itokawa et al. and Naruse et al. The present invention is therefore not obvious over Itokawa et al. or Naruse et al. combined with Vater et al. Withdrawal of the rejection is therefore respectfully requested.

Should the Examiner have any questions regarding the present application, she is requested to please contact MaryAnne Armstrong, PhD (Reg. No. 40,069) in the Washington DC area at (703) 205-8000.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §1.16 or under 37 C.F.R. §1.17; particularly, extension of time fees.

Respectfully submitted,

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